Anesthesia Case of the Month

History

A 15.5-kg (34-lb) 3-year-old neutered male Rat Terrier was evaluated for surgical correction of medial luxation of the left patella. The owner did not report any previous medical conditions, and the dog had been anesthetized for castration without incident at 6 months of age. Physical examination findings were unremarkable other than grade 3 of 4 luxation of the left patella and associated lameness. Results of a CBC and serum biochemistry panel were unremarkable.

Food was withheld from the dog overnight, and the dog was premedicated with hydromorphone (0.09 mg/kg [0.04 mg/lb], IM) and dexmedetomidine (2.3 µg/kg [1 µg/lb], IM). An 18-gauge IV catheter was placed in the right cephalic vein once the patient was adequately sedated. Preoxygenation was accomplished by application for 5 minutes of a face mask without the diaphragm that was attached to an anesthesia machine by means of an adult noncoaxial rebreathing circuit. A lead II ECG waveform was monitored throughout the anesthetic induction period. Constant rate infusions of morphine (0.25 mg/kg/h [0.11 mg/lb/h], IV), lidocaine (51 µg/kg/min [23.2 µg/lb/min], IV), and ketamine (10.3 µg/kg/min [4.7 µg/lb/min], IV) were initiated, and anesthesia was induced with propofol (3.9 mg/kg [1.8 mg/lb], IV, to effect). Orotracheal intubation was accomplished with a 9.5-mm (internal diameter) endotracheal tube. General anesthesia was maintained with a partial IV technique consisting of administration of sevoflurane in oxygen and the CRIs as described. A balanced crystalloid fluid was also administered (10.3 mL/kg/h [4.7 mL/lb/h], IV).

The patient was monitored continuously by a dedicated anesthesia technician. Monitoring included measurement of SpO₂, PETCO₂, respiratory rate, blood pressure (determined by use of a noninvasive, oscillometric method), and rectal temperature. In addition, a lead II ECG was monitored continuously for heart rate and rhythm. The patient breathed spontaneously, and all values were within acceptable limits with the exception of SpO₂, which was 94%.

Prior to the initial surgical incision, lidocaine (3.89 mg/kg [1.77 mg/lb]) was injected into the left stifle joint and cefazolin (22 mg/kg [10 mg/lb]) and famotidine (0.5 mg/kg [0.23 mg/lb]) were administered IV. Immediately after making the initial incision, the surgeon observed that blood at the surgical site was subjectively dark. The anesthesiologist was called to the suite, and it was noted that the SpO₂ was 92% and the oximeter was displaying normal waveforms. Further evaluation suggested that the patient was adequately anesthetized (ie, absent palpebral reflex, ventromedial eye position, and moderate jaw tone) with pale pink to slightly cyanotic mucous membranes and capillary refill time of < 2 seconds. Peripheral pulses were easily palpable in the palmar digital arch and lingual artery. Five minutes later, heart rate was 88 beats/min with a normal rhythm, respiratory rate was 11 breaths/min, PETCO₂ was 37 mm Hg, systolic arterial blood pressure was 119 mm Hg, diastolic arterial blood pressure was 80 mm Hg, mean arterial blood pressure was 93 mm Hg, rectal temperature was 36.6°C (97.9°F), and SpO₂ was 90%.

Potential causes of hypoxemia were investigated. Although a gas analyzer was not available, oxygen pressure in the central supply line was 92 psi, and the flow meter on the anesthesia machine indicated an O₂ flow rate of 1 L/min. Other patients anesthetized at the same time did not have evidence of oxygen supply issues. Inspection of the equipment and the capnogram confirmed that the anesthesia machine and breathing circuit were connected appropriately. The distal end of the endotracheal tube was palpable at the thoracic inlet, and manual positive-pressure ventilation resulted in appropriate, quiet bilateral lung sounds. An arterial blood gas sample was obtained from the auricular artery and submitted for blood gas analysis, which revealed pH of 7.415, PaO₂ of 33.4 mm Hg, PaCO₂ of 489 mm Hg, base excess of –2 mmol/L, total CO₂ of 23 mmol/l, and SaO₂ of 100%.

Question

What is the likely cause of the difference between the SpO₂ (90%) and SaO₂ (100%) values?

Answer

The difference in oxygen saturation values obtained by means of pulse oximetry versus blood gas analysis of arterial blood was most likely a result of the presence of a dyshemoglobin, specifically methemoglobin. Intermittent positive-pressure mechanical ventilation was initiated, and because other vital signs were stable, the surgeon finished the planned procedure. Total surgical time was 26 minutes. After closure of the...
Hemoglobin is the metalloprotein responsible for most oxygen transport in the blood, increasing oxygen-carrying capacity of the blood some 70-fold, compared with dissolution in plasma alone. Methemoglobin is hemoglobin in which the iron in the heme moiety in one or more of the hemoglobin subunits has been oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Oxygen cannot bind to the deoxy (Fe^{2+}) form of hemoglobin; thus, the oxygen-carrying capacity of the blood is decreased in patients with methemoglobinemia. In addition, as a result of allosteric interactions among the remaining heme groups, methemoglobin formation leads to decreased release of oxygen at the tissue level, shifting the oxygen dissociation curve to the left and changing the shape from sigmoidal to hyperbolic.

Oxidation of hemoglobin occurs spontaneously, with naturally occurring methemoglobin concentrations of approximately 2% found in dogs, and an endogenous mechanism exists to return methemoglobin to its functional state. Methemoglobin reductase (also known as cytochrome b, reductase or nicotinamide adenine dinucleotide diaphorase) is the enzyme responsible for reducing methemoglobin to hemoglobin.

Methemoglobinemia is an excess of methemoglobin in the blood and should be suspected when more common causes of cyanosis and dark blood have been ruled out and results of pulse oximetry and arterial blood gas analysis are discordant. Methemoglobinemia can be congenital or acquired. Acquired methemoglobinemia is caused by the oxidant actions of certain drugs or toxins and has been reported in veterinary species in association with acetaminophen, benzocaine, phenaazopyridine, hydroxyurea, chlorate herbicides, red maple leaf, nitrate or nitrate preservatives, and sulfates. Benzocaine laryngeal sprays are frequently implicated in the development of methemoglobinemia and subsequent death in cats, and their use should be abandoned. In humans, multiple local anesthetics, including prilocaine, tetracaine, and lidocaine, in addition to benzocaine, have been reported to induce clinically relevant concentrations of methemoglobin, although the effectiveness of lidocaine in oxidizing hemoglobin is particularly controversial.

Congenital methemoglobinemia due to a deficiency of the methemoglobin reductase enzyme has been reported in humans, dogs, and cats. Other types of congenital methemoglobinemia are documented in humans, including that due to an abnormal quaternary form of hemoglobin (hemoglobin M), but this has not been reported in other species.

Methemoglobin is a dark pigment that classically causes blood to appear chocolate brown and results in cyanosis. For patients suspected to have methemoglobinemia, a cageside test can be performed comparing the color of the patient's blood with that of a control animal (Figure 1). Additionally, methemoglobin will stay dark if oxygen is blown over the sample, whereas deoxygenhemoglobin will brighten.

The term oxygen saturation refers to the percentage of total hemoglobin in the blood capable of transporting oxygen, and 3 methods exist for determining oxygen saturation: pulse oximetry, arterial blood gas analysis, and CO-oximetry. In healthy patients, oxygen saturation (Spo\textsubscript{2} and SaO\textsubscript{2}) is approximately equivalent to the fraction of hemoglobin that is oxygenated. However, pulse oximetry readings (Spo\textsubscript{2}) in patients with methemoglobinemia may be misleading because the results trend toward 85%. Traditional pulse oximeters calculate the ratio of oxygenated hemoglobin to oxygenated plus deoxygenated hemoglobin by measuring the absorbance of 2 specific wavelengths of light: 660 nm (red light) and 940 nm (near infrared light). Oxygenated hemoglobin absorbs more infrared than red light, whereas deoxygenated hemoglobin absorbs more red than infrared light. The pulse oximeter measures the absorbance of the emitted light, subtracts...
background nonpulsatile absorbance, then uses an algorithm to calculate oxygen saturation. However, this algorithm ignores dyshemoglobins that cannot carry O2, such as methemoglobin and carboxyhemoglobin. Methemoglobin has the same absorption coefficients for light of both 660- and 940-nm wavelengths, and for many pulse oximeters, an absorbance ratio of 1.0 corresponds to an oxygen saturation of approximately 89%. Thus, SpO2 values in patients with methemoglobinemia may not reflect the true fraction of hemoglobin that is oxygenated.

The hemoglobin oxygen saturation value obtained by means of blood gas analysis (SaO2) will also be inaccurate in the presence of methemoglobinemia. Arterial blood gas analyzers calculate SaO2 from the measured PaO2 and pH and will overestimate hemoglobin saturation in patients with methemoglobinemia.

In contrast to pulse oximeters and blood gas analyzers, CO-oximeters use multiple diodes and wavelengths of light to measure the fraction of hemoglobin that is oxygenated (ie, the ratio of oxygenated hemoglobin to the sum of all hemoglobin forms [oxygenated hemoglobin, deoxyhemoglobin, methemoglobin, carboxyhemoglobin, and sulfhemoglobin]), rather than oxygen saturation. Although portable pulse CO-oximeters are now available, they were not in use at our hospital at the time of this report.

CO-oximeters can also be used to measure the fraction of methemoglobin in the blood, and a specific assay of methemoglobin reductase activity in veterinary patients is now available. For the dog of the present report, testing for confirmation of a methemoglobin reductase deficiency was not pursued for several months after the anesthetic event. However, it was considered unlikely that the methemoglobinemia in this patient was caused by a toxicosis because of the lack of exposure to known toxins. In addition, the owner denied administration of medications or supplements at home. Lidocaine has been sporadically implicated in the human literature as a possible cause of methemoglobinemia, and the patient of the present report received a lidocaine CRI during the perioperative period and an intra-articular injection of lidocaine prior to the initial surgical incision. However, in many of the reported human cases, other oxidant drugs have also been administered or the patient is a young child with potentially immature metabolic systems. In addition, the blood sample used to measure the methemoglobin fraction in this dog was collected 10 days after the anesthetic event, by which time toxic methemoglobinemia should have resolved. Species differences in methemoglobin reductase activity exist, and dogs may be relatively deficient, compared with humans and nonhuman primates. In adult sheep, the effective half-life of methemoglobin is 125 minutes, whereas adult humans reduce methemoglobin more slowly, with a half-life of 162 minutes; reduction of methemoglobin by human neonates is even more prolonged, with a half-life of 210 minutes.

There are numerous reports of the intraoperative diagnosis of methemoglobinemia in the human literature. Most of these cases are associated with use of benzocaine or the antibacterial agent dapsone, although the diagnosis of congenital methemoglobinemia in the perioperative period in humans has been occasionally reported. In dogs, a single case report exists of the diagnosis of congenital methemoglobinemia during general anesthesia. Many suspected cases of methemoglobinemia in veterinary medicine are first discovered when dark blood is noticed during a routine surgical event.

If methemoglobinemia is suspected prior to or during general anesthesia, the focus should be on optimizing oxygen delivery via appropriate cardiovascular and respiratory support. More common causes of cyanosis and low SpO2 values should be ruled out, including equipment issues, endobronchial intubation, apnea, pneumothorax, and lower airway disease. Any drugs with oxidant tendencies should be avoided or discontinued. Consideration should be given to placement of an arterial catheter for invasive blood pressure monitoring and arterial blood gas analysis. Preoxygenation by means of mask administration of oxygen before anesthetic induction should be routine for all patients but may be especially important for those with congenital methemoglobin reductase deficiency.

The treatment for toxic methemoglobinemia is IV administration of methylene blue. Not all patients with methemoglobinemia will require this treatment, and many otherwise healthy patients will do well with supportive care alone. Infusion of methylene blue (1 to 2 mg/kg [0.45 to 0.9 mg/lb]) should be considered when high fractions (> 30% to 40%) of methemoglobin are present or cardiorespiratory complications develop. Methylene blue is reduced to leucemethylene blue, which then converts methemoglobin to hemoglobin. It should be noted that high doses of methylene blue can paradoxically oxidize hemoglobin and cause hemolysis with Heinz bodies. Other antioxidants, including N-acetylcysteine and ascorbic acid, may also be considered in the treatment of methemoglobinemia, especially when it develops secondary to toxin exposure.

References


JAVMA, Vol 242, No. 6, March 15, 2013 Vet Med Today: Anesthesia Case of the Month

Unauthenticated | Downloaded 11/26/23 11:49 PM UTC


